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protection to a patient in need thereof, wherein the antibodies block binding of enterohemorrhagic *E. coli* to a mammalian cell.

Please add new claims 64-65 as follows:

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--64. The method of claim 60, wherein the anti-intimin antibodies are monoclonal.

65. The method of claim 60, wherein the anti-intimin antibodies are polyclonal.--

REMARKS

Claim 60 has been amended, and claims 64 and 65 have been added. Therefore, claims 60, 64, and 65 are currently pending. Claims 64 and 65 more precisely define the antibodies used in the method of claim 60. The support for polyclonal and monoclonal antibodies as inherent to "antibodies" is found in the specification and is well known in the art. Additionally, claim 60 has been amended to recite "an amount of isolated anti-intimin antibodies effective to provide passive immune protection" to correlate with the preamble of the claim. Support for "blocking antibodies" occurs in the specification at page 78, item F, and page 84, item 3. As such, these amendments introduce no new matter, and Applicants respectfully request their entry.

Rejections Under 35 U.S.C. §112, First and Second Paragraphs

The Office rejected claim 60 as allegedly nonenabled under Section 112, first paragraph, asserting that undue experimentation would be required to produce a passive immune protection response, and further noting that no working examples are presented "with the missing information." Office Action at page 3.

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Applicants respectfully traverse the Office's position. First, the Office asserts that "the portion of intimin to which the antibodies bind would need to be clearly set forth in order to obtain the desired protective effect of preventing infection through blocking (either partial or complete) of receptor association." Office Action at page 3. Applicants note that the blocking effect of an antibody can be ascertained without knowing its specific binding epitope. The specification sets forth exact procedures to determine binding and blocking of binding, which are distinct from the teaching of Chart et al. Applicants respectfully submit this binding assay is well within the ordinary skill of one in the art and does not constitute undue experimentation.

The Office also rejected claim 60 as allegedly indefinite because the claim language was not correlated with the preamble. Applicants have addressed this rejection by amending claim 60 to recite "an amount of isolated anti-intimin antibodies effective to provide passive immune protection" to correlate with the preamble of the claim. Applicants respectfully request reconsideration of these rejections in light of these arguments and amendments.

Rejection Under 35 U.S.C. §102(b)

The Office rejected claim 60 as allegedly anticipated by Craviato et al. (*J. Inf. Disease* **163**:1257-1255 (1991). Applicants respectfully traverse this assertion, on the basis that Craviato fails to teach every element of the claims as amended. Cravioto's secretory IgA is derived from natural human colostrum and therefore cannot be "isolated anti-intimin antibodies" as required by claim 60 as amended. Cravioto does not teach intimin and does not teach the blocking of enterohemorrhagic *E. coli*. Carried to its logical conclusion, the Office's position would be that all polyclonal antibodies are unpatentable, because some human has been exposed to that antigen

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at some time. Thus, according to this position, human blood would anticipate all polyclonal antibodies. Applicants submit that such a conclusion is unsupportable.

In fact, Cravioto notes that "[t]he specific inhibitory capacity of total breast milk against EPEC strains infecting infants at an early age is probably due to the presence of many factors including the ones studied here." Cravioto at page 1253 (emphasis added). The Office quotes that "oligosaccharides and sIgA could represent two of the most important protective fractions," but fails to indicate how a teaching of oligosaccharides, sIgA, and other factors in breast milk would inherently lead to an administration of isolated anti-intimin antibodies providing a protective effect.

Further, Cravioto does not actually teach administering an isolated immunoglobulin to a patient. Cravioto investigated "[t]he question remaining . . . [of] whether this protection [of infants against diarrhea] is afforded by the intake of specific factors present in breast milk or by the process of breast-feeding as a part of a larger cultural context related to child-rearing practices." Cravioto at page 1247. Neither Applicants nor anyone else would dispute Cravioto's closing statement (partially quoted by the Office) that "[t]he possibility of selectively incrementing specific immunoglobulins in breast milk (or the addition of certain oligosaccharides to cow's milk . . .) could increase the value of these products as a vehicle for protection against enteric infections in infants born in developing countries." Cravioto page 1253 (emphasis added). This statement does not, however, lead anyone to the selection of isolated anti-intimin antibodies, or to the blocking of binding of EHEC to mammalian cells, or to methods of administering such antibodies.

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Finally, Cravioto only studied enteropathogenic *E. coli* (EPEC). Cravioto cannot be said to provide blocking of EHEC to mammalian cells, because EHEC was not studied. Therefore, because Cravioto fails to teach intimin, fails to teach isolated anti-intimin antibodies, fails to teach administration, and fails to teach blocking of binding of EHEC to mammalian cells, Cravioto fails to anticipate the instant invention.

The Office rejected claim 60 as allegedly anticipated by Ashkenazi et al. (*J. Pediatr.* **113**:1008, abstract only). Applicants respectfully traverse this assertion, noting that Ashkenazi fails to teach every element of the claimed invention. Applicants also disagree with the Office's use of "inherency" based on Agin et al. (*Cytokines, Cholera and the Gut*, p. 315-320 (1995)). First, new claim 64 recites monoclonal antibodies, which are not taught by Agin et al. Second, Agin et al. and Ashkenazi et al. do not teach isolated anti-intimin antibodies. Ashkenazi et al. teach only that "[i]ntervenously administered immune globulin (IVIG) therapy has been reported to be beneficial in a few children with HUS." *See* abstract Ashkenazi et al. This disclosure is not enabling for isolated anti-intimin antibodies, since intimin is not taught. Furthermore, a method of isolating such anti-intimin antibodies (should such antibodies be hypothetically present) is also not taught by Ashkenazi et al.

Ashkenazi et al. also fails to teach blocking of binding of enterohemorrhagic *E. coli* to a mammalian cell. It is inappropriate to generalize a method of action from showing some benefit in a few children with one syndrome to a specific physiologic action. Ashkenazi et al. merely outlines a desire in the field to provide some treatment to sick children, but does not teach a method of administering one particular kind of isolated antibodies to one particular protein, i.e., intimin. Agin et al. also fails to address this issue. In fact, Agin et al. state that "little is known

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about the role anti-intimin antibodies play in recovery or protection from disease" and their study was an attempt "to determine **if there was a correlation** between prior exposure to intimin and protection from disease." Emphasis added, Agin et al. at 316. Absent a demonstration of causation, the teachings of Agin et al. do not anticipate Applicants' claimed method of treatment with isolated anti-intimin antibodies. Even Agin et al. realized this, stating that "[i]n future studies, it will be necessary to identify the role of anti-intimin antibodies and determine if these antibodies protect from a virulent challenge." Agin et al. at 318. Finally, neither Agin et al. nor Ashkenazi et al., alone or in combination, teach blocking of binding of EHEC to a mammalian cell. Therefore, neither reference, alone or in combination, anticipates Applicants' claimed invention.

Rejection Under 35 U.S.C. §103

The Office rejected claim 60 as allegedly obvious in view of Isberg et al. (U.S. Pat. No. 5,310,654) and Pace et al. (U.S. Pat. No. 5,681,736) (hereinafter "Pace '736") for the recitation of anti-invasin antibodies. Applicants respectfully note that neither reference teaches blocking of binding of EHEC to a mammalian cell. Merely proposing protective efficacy does not teach the blocking of a particular pathogen to the mammalian cell. Further, neither reference teaches that an anti-invasin antibody would block binding of *E. coli*. Indeed, the teachings of the references themselves show that Applicants' invention would not have been obvious or have had a reasonable expectation of success as suggested in the Office Action.

For example, although the Office states that a "person of ordinary skill in the art would have been motivated by the reasonable expectation of success of providing a passive immune

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protection to a patient through administering anti-intimin [sic, anti-invasin] (Ipa)" (Office Action at 8), Pace '736 notes that "Ipa proteins are logical vaccine candidates although **their protective efficacy has not been clearly established**," and "though a number of vaccine candidates for *Shigella* have been tested in animals and humans, **a successful one has not been found**." Emphasis added, Pace '736, col. 3, lines 26-27 and 39-41. Because these methods were not effective, the Office's suggestion that they inherently block binding of EHEC to mammalian cells seems improbable. Pace '736 in fact underscored the need in the art for a method of providing a protective immune response, noting that "[v]accines against many enteric pathogens . . . are not yet available but the epidemiology of these disease agents makes such vaccines an important goal." Pace et al., col. 3, lines 6-9.

Isberg teaches that "invasive organisms may be used to prepare antisera for passive immunization. Thus, γ-globulin could be prepared which has antibodies to a broad spectrum of pathogens and for strains of a particular pathogen." Isberg, column 7, lines 11-14. Thus, while Isberg teaches antibodies to invasive organisms, Isberg fails to recite a single protein as an antigen, let alone the intimin of Applicants' method. Further, Isberg was unconcerned with treatment of patients, and with amounts of antibodies effective to provide passive immune protection to a host in need thereof. For all of these reasons, Isberg fails to render obvious Applicants' claimed method of providing passive immune protection comprising administering an amount of isolated anti-intimin antibodies effective to provide passive immune protection to a patient in need thereof, wherein the antibodies block binding of enterohemorrhagic *E. coli* to a mammalian cell.

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In view of the forgoing amendments and arguments, Applicants respectfully request reconsideration of the rejections and timely allowance of the claims.

Please grant any additional extensions of time required to enter this response and charge any additional required fees to our deposit account 06-0916.

Respectfully submitted,

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